UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,229	07/15/2003	Juan Jose Legarda Ibanez	55979-0100	1190

23370 7590 02/22/2007

JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
ATLANTA, GA 30309

EXAMINER	
KIM, JENNIFER M	
ART UNIT	PAPER NUMBER
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,229	IBANEZ, JUAN JOSE LEGARDA	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-30 and 46-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-30 and 46-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 29, 2007 has been entered.

Action Summary

The rejection of claims 17-26, 29, 46-55 and 58 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 1,3-6 and 8-13 and 28 of copending Application No. 11/111,435 is being maintained for the reasons stated in the previous Office Action and the rejection is modified in this Office Action to include newly added claims.

The rejection of claims 17-26 and 29 under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record is being maintained for the reasons stated in the previous Office Action.

The rejection of claims 27 and 28 under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record as applied to claims 17-26 and 29, above, and further in view of Opitz (U.S.Patent No. 5,519,017) is maintained for the reasons stated in the previous Office Action.

The rejection of claims 30, 46-55 and 58 under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record as applied to claims 17-26 and 29 above, and further in view of Aguirre et al. (Alcohol, 1990) is hereby expressly withdrawn in view of Applicant's persuasive argument regarding **Aguirre et al.** that a simple observation that b-endorphin levels are lower in alcoholics in no way implies that increasing b-endorphin levels would eliminate the cause of alcohol consumption and that many diseases and conditions cause a change in a biological marker, however this does not mean to one of ordinary skill in the art that reversing the levels of the biological marker inherently treats a disease. However, upon further consideration, a new ground(s) of rejection is made as follows:

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claims 30, 46-55 and 58-68 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view

of Nutt et al. (Alcohol & Alcoholism, 1993) of record as applied to claims 17-26 and 29 below (see page 8 of instant Office Action), and further in view of Soderpalm et al. (1998).

The teachings of Gerra et al. and Nutt et al. as applied as before. (see page 8 of instant Office Action).

Neither Gerra et al. nor Nutt et al. teach the reduction of desire to drink alcohol by flumazenil.

Soderpalm et al. teach that it is suggested that benzodiazepines, by acting on GABA receptors, facilitate ethanol intake by increasing ethanol's taste hedonic properties. (Abstract, last sentence). Soderpalm et al. suggested that the agonist acts on the benzodiazepine binding site of the GABA receptor increase the attractiveness of ethanol. (page 220, left-hand side, last paragraph, first sentence). Soderpalm et al. again, suggest that benzodiazepines stimulate alcohol intake and alcohol palatability. (page 220, last paragraph, first sentence). Soderpalm et al. teach that the increased hedonic response to ethanol was **blocked by pretreatment with the benzodiazepine receptor antagonist flumazenil.** (abstract, second to the last sentence).

It would have been obvious to one of ordinary skill in the art at the time the invention was made that the employment of flumazenil for the treatment of alcohol dependency as modified by Nutt et al. would result in the reduction in desire to drink alcohol because Soderpalm et al. teach that increased hedonic taste of ethanol involving palatability was blocked by the pretreatment of flumazenil, and that flumazenil is benzodiazepine receptor antagonist taught by Soderpalm et al. that antagonizes or

blocks ethanol's taste hedonic properties. One would have been motivated to employ flumazenil as taught by Gerra et al. as modified by Nutt et al. for the treatment of alcohol dependency to reduce the alcohol desire in order to achieve an expected benefit of flumazenil's GABA receptor antagonizing properties including blocking positive palatability or taste of ethanol.

Claim 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record and further and further in view of Soderpalm et al. (1998) as applied to claims 30, 46-55 and 58-68 and 71 above, and further in view of Opitz (U.S.Patent No. 5,519,017).

The teachings of Gerra et al., Nutt et al., and Soderpalm et al. as applied as before.

Above references do not teach the specified additional agent set forth in claims 56 and 57.

Opitz reports that clomethiazole, piracetam and disulfiram are the drugs used to control the influence of alcohol and the alcoholism and that clomethiazole is used for the alcoholic delirium, piracetam is used for the palliatives or the acute alcohol withdrawal and disulfiram is the most frequently used for the treatment of alcoholism. (column 1, lines 37-55).

It would have been obvious to one of ordinary skill in the art to employ other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of

alcohol dependency taught by Gerra et al. as modified by Nutt et al. and Soderpalm et al. One would have been motivated to incorporate other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency in order to achieve at least an additive effect in treatment to alcohol dependency and achieve the expected benefit of the palliative or anti delirium effect of the each of the agent in alcohol withdrawn treatment. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)) in treatment of alcoholism.

Claims 69 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) and further in view of Soderpalm et al. (1998) as applied to claims 30, 46-55 and 58-68 and 71 above and, further in view of Opitz (U.S.Patent No. 5,519,017) of record.

The teachings of Gerra et al, Nutt et al, and Soderpalm et al. as applied as before.

Above references do not teach the specified additional agent set forth in claims 69 and 70.

Opitz reports that clomethiazole, piracetam and disulfiram are the drugs used to control the influence of alcohol and the alcoholism and that clomethiazole is used for the alcoholic delirium, piracetam is used for the palliatives or the acute alcohol withdrawal

and disulfiram is the most frequently used for the treatment of alcoholism. (column 1, lines 37-55).

It would have been obvious to one of ordinary skill in the art to employ other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency taught by Gerra et al. as modified by Nutt et al. and Soderpalm et al. One would have been motivated to incorporate other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency in order to achieve at least an additive effect in treatment to alcohol dependency and achieve the expected benefit of the palliative or anti delirium effect of the each of the agent in alcohol withdrawn treatment. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)) in treatment of alcoholism.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-26, 29, 46-55 and 58-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 1,3-6 and 8-13 and 28 of copending Application No. 11/111,435. The instant application and copending application are directed to same subject matter comprising treatment of alcohol dependency such as alcohol abuse with same effective daily dose with administration of same active agent (flumazenil). Instant claims differ by amounts sequentially administered and the time intervals. However, the amounts of daily dosages divided to sequentially administer to the patient and the time intervals are obvious modification since they are within the knowledge of one of ordinary skill in the art. One of ordinary skill in the art would optimize the dosing intervals and to divided known daily dosage of treating alcohol dependency according to patient's condition, severity and the factors concerning concurrent medical ragmen.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17-26 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record.

Gerra et al. teach ethanol addicts with dependency were treated with flumazenil in dose of **2mg/day divided into four doses** (0.5mg per dose) **IV (intravenous, parenteral) every 6 hours** (sequential) for 48 hours. (Abstract, page 63 lines 32-33). Gerra et al. teach that significant improvement in **alcohol withdrawal symptoms including tremors, sweating, nausea, depression anxiety and restlessness** shown by data when the patients were treated with flumazenil. (page 65 lines 7-10). Gerra et al. teach that some patients experienced **somnolence** during first day of the treatment with flumazenil. (page 65, first full paragraph).

Gerra et al. do not teach the specified time intervals and the specified portion of amounts set forth in claims 17, 19, 20 and 24 administering flumazenil under sedation set forth in claims 29 and 43 and administering additional agent set forth in claim 26.

Nutt et al. teach that **2mg dose** of flumazenil was administered as an **IV infusion** over **1 minute** to alcoholics in acute withdrawal. (abstract, page 338, 3rd and 4th full paragraphs). Nutt et al. teach that the other drug (additional agent) was administered after flumazenil. (page 338, 4th paragraph).

It would have been obvious to one of ordinary skill in the art to optimize the time intervals and dividing portions of known daily effective dose of flumazenil 2mg/day

taught by Gerra et al. because flumazenil is effective for the treatment of symptoms of alcohol dependency in divided doses and administered in time intervals of 6 hours by Gerra et al. and Nutt et al. teach that flumazenil can also be administered over 1 minute. These references teach the extension of time intervals of flumazenil can be 1 minute to 6 hours. Accordingly, one would have been motivated to optimize the well-known effective daily dose of flumazenil for the treatment of alcohol dependency within any time intervals between 1minutes taught by Nutt et al. to 6 hour time period taught by Gerra et al. in any divided total daily dose for the treatment of alcohol dependency because as anyone of ordinary skill in the art will appreciate, preferred divided dosages and intervals are merely exemplary and serve as useful guideposts for the physician. There are, however, many reasons for varying dosages, and dosing intervals including by orders of magnitude; for instance, a patient having multiple dosing regimen or one having noncompliant would require a correspondingly dosing intervals. Furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as toxicity. One would have been motivated to optimize the dosing intervals and optimize the daily amounts in portions to achieve an ultimate therapeutic regimen needed for individual patient's medical requirements.

With regard to administration of flumazenil under sedation set forth in claims 29 and 43, it would have been obvious to one of ordinary skill in the art to administer flumazenil, particularly while the patient is in sleep (sedation) because flumazenil causes somnolence as taught by Gerra et al. One would have been motivated to employ flumazenil while the patient is in sleep in order to take an advantage of side

effect of flumazenil causing somnolence reported by Gerra et al. to achieve an additive benefit of somnolence while patient is in sleep. One would have been motivated to employ flumazenil while the patient is in sleep in order to conveniently take advantage of somnolence effect of flumazenil.

With regard to administration of additional agent after the administering flumazenil for the treatment of alcohol dependency is obvious because Nutt et al. teach that other agent (additional agent) is routinely administered after flumazenil in treatment of Nutt et al. One would have been motivated to employ additional agent for the treatment of alcohol dependency taught by Gerra et al. as modified by Nutt et al. in order to achieve routine effect of ameliorating alcohol dependency as taught by Nutt et al.

Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record as applied to claims 17-26 and 29 above, and further in view of Opitz (U.S.Patent No. 5,519,017).

The teachings of Gerra et al. and Nutt et al. as applied as before.

Gerra et al. and Nutt et al. do not teach the specified additional agent such as clomethiazole set forth in claims 27, 41 and piracetam and disulfiram set forth in claims 28 and 42.

Opitz reports that clomethiazole, piracetam and disulfiram are the drugs used to control the influence of alcohol and the alcoholism and that clomethiazole is used for the

alcoholic delirium, piracetam is used for the palliatives or the acute alcohol withdrawal and disulfiram is the most frequently used for the treatment of alcoholism. (column 1, lines 37-55).

It would have been obvious to one of ordinary skill in the art to employ other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency taught by Gerra et al. as modified by Nutt et al. One would have been motivated to incorporate other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency in order to achieve at least an additive effect in treatment to alcohol dependency and achieve the expected benefit of the palliative or anti delirium effect of the each of the agent in alcohol withdrawn treatment. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)) in treatment of alcoholism.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Response to Arguments

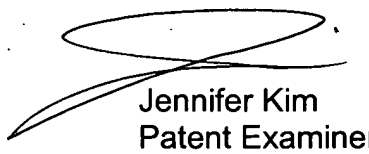
Applicant's arguments filed January 29, 2007 have been fully considered but they are not persuasive. Applicant argues, regarding claims 17-26, 29, 31-40, 43 and 45, that Gerra and Nutt, alone or together do not in any way disclose, suggest or provide motivation to one of ordinary skill in the art to administer flumazenil in order to reduce the desire to drink alcohol. This is not persuasive because the claims are rejected based on their limitation of treating alcohol dependency not the limitation of "reducing the desire to drink alcohol" which is not included in the rejected claims. Applicant argues that the Gerra and Nutt methods are directed toward treating alcohol withdrawal symptoms not treating alcohol dependency and that Gerra and Nutt do not mention, hint, suggest or provide motivation for a skilled artisan to administer flumazenil in order to treat alcohol dependency. This is not persuasive because the distinction between withdrawal symptoms and alcohol dependency do not alter that fact that the same compound (flumazenil) has been previously used by Gerra et al. to treat alcohol addicts with dependency having withdrawal symptoms. The patient (alcohol addicts), condition (dependency with withdrawal symptoms) to be treated are the same. An explanation of why that symptoms/conditions differ in the same patient does not make unobvious the same treatment of the same conditions encompassed by the claims. Applicant argues that treating alcohol withdrawal symptoms with flumazenil does not inherently anticipate treating the cravings or desire to drink alcohol or treating alcohol dependency. This is not persuasive because in this case, it is obvious to one of ordinary skill in the art to employ flumazenil for the treatment of alcohol dependency as modified by Nutt et al. would result in the reduction in desire to drink alcohol because Soderpalm et al. teach

that palatability of ethanol was blocked by the treatment of flumazenil. Applicant argues that the dosage regimens described by the prior art, neither reference alone or in combination, teaches, suggests or provides motivation to use a smaller amount of flumazenil administered sequentially over 1 to 5 minutes for any purpose. This is not persuasive because the dosing ranges of flumazenil on alcohol addicts with dependency having withdrawal symptoms extend from 1 minutes to 6 hours as taught by each of the references. Therefore, it would have been obvious to one of ordinary skill in the art to optimize the well-known dosing intervals between 1 minute to 6 hours time period in any divided daily dose for the effective treatment without surprising and unexpected result. Applicant argues with regarding Opitz reference that Opitz teaches away from using disulfiram to reduce the desire to drink alcohol. This is not persuasive because Opitz simply teaches the usefulness of clomethiazole, piracetam and disulfiram for the treatment of alcoholism and alcoholism. Therefore, it would have been obvious to one of ordinary skill in the art to employ the other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency taught by Gerra et al. as modified by Nutt et al and Soderpalm et al. Applicant's argument regarding Aguirre reference is moot because Aguirre reference is withdrawn as a reference. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Jennifer Kim
Patent Examiner
Art Unit 1617

Jmk
February 15, 2007